Complete Summary

GUIDELINE TITLE

U.S. Public Health Service guideline on infectious disease issues in xenotransplantation.

BIBLIOGRAPHIC SOURCE(S)

U.S. Public Health Service guideline on infectious disease issues in xenotransplantation. Centers for Disease Control and Prevention. MMWR Recomm Rep 2001 Aug 24;50(RR-15):1-46. [131 references]

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY

SCOPE

DISEASE/CONDITION(S)

Xenogeneic infectious diseases that may be associated with xenotransplantation

GUIDELINE CATEGORY

Prevention

CLINICAL SPECIALTY

Infectious Diseases
Pathology
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Clinical Laboratory Personnel

Health Care Providers
Nurses
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

- To present measures that can be used to minimize the risk of human disease due to xenogeneic infectious agents including both recognized zoonoses and non-zoonotic infectious agents that become capable of infecting humans due to the unique facilitating circumstances of xenotransplantation.

TARGET POPULATION

- Individuals undergoing xenotransplantation
- Health care workers and others in close contact with the xenotransplant recipient

INTERVENTIONS AND PRACTICES CONSIDERED

Xenotransplantation Protocol Issues

1. Formation of the xenotransplantation team (physicians, veterinarians, others with infectious disease experience).
2. Establishment of clinical xenotransplantation sites which utilize U.S. Clinical Laboratory Improvements Act 1988 accredited virology and microbiology laboratories.
3. Ensuring adequate institutional review of xenotransplant clinical trial protocols.
4. Development of clearly defined methodologies for pre-xenotransplant health screening and post-xenotransplant surveillance of recipients.
5. Obtaining and documenting informed consent and patient education on the risks involved in xenotransplant.

Animal Sources for Xenotransplantation

1. Reducing risk of infection transmission by exercising precautions in animal procurement and processing procedures.
2. Maintaining source animal facilities according to principles that minimize introduction and spread of infectious agents.
3. Pre-xenotransplantation screening of source animals and/or cells or tissues for known infectious agents.
4. Herd/colony health maintenance and surveillance for infectious agents, including routine serum samples and maintenance of a subset of sentinel animals.
5. Individual source animal screening and qualification through documentation of breed/lineage, general health, and vaccinations; establishing quarantine period for candidate source animals.
6. Procurement and screening of nonhuman animal live cells, tissues or organs used for xenotransplantation using procedures that minimize contamination.

7. Maintaining archives of source animal medical records and specimens for defined periods.
8. Disposal of animals and animal by-products.

Clinical Issues

1. Lifelong surveillance of xenotransplantation product recipient for infectious diseases.
2. Archival of biological specimens of xenotransplant product recipient for public health investigations.
3. Strict adherence to infection control practices, including procedures for handling/disinfection of equipment and infectious wastes; identification of the etiology of infections in the xenotransplant recipient; education, surveillance, and post-exposure evaluation of health care workers who provide post-xenotransplantation care.
4. Maintaining cross-referenced health care records linking all relevant records concerning the xenotransplant product recipient, the xenotransplant product, source animals and procurement centers, and significant nosocomial exposures.

Public Health Needs

1. National xenotransplantation database.
2. Biologic specimen archives.
3. U.S. Secretary for Health and Human Service's Advisory Committee on Xenotransplantation.

MAJOR OUTCOMES CONSIDERED

- Risk of zoonotic infection of xenotransplantation product recipients
- Risk of subsequent transmission of zoonotic infection to recipients' families, healthcare workers and other close contacts, and the general public

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not applicable

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

On September 23, 1996, the U.S. Department of Health and Human Services (DHHS) published for public comment the document titled â œDraft Public Health Service (PHS) Guideline on Infectious Disease Issues in Xenotransplantationâ to address the infectious disease concerns raised by xenotransplantation (61 U.S. Federal Register 49919). The draft guideline was jointly developed by five components within the U.S. Department of Health and Human Services --- the Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Health Resources and Services Administration (HRSA), National Institutes of Health (NIH), all parts of the United States Public Health Service (PHS), plus the U.S. Department of Health and Human Services Office of the Assistant Secretary for Planning and Evaluation.

In response to the draft guideline, the U.S. Department of Health and Human Services received over 140 written comments reflecting a broad spectrum of public opinion (U.S. Federal Register docket No. 96M-0311). Comments were received from a variety of stakeholders, including representatives of academia;

industry; patient, consumer, and animal welfare advocacy organizations; professional, scientific and medical societies; ethicists; researchers; other government agencies and private citizens.

In revising the draft guideline, careful consideration was given to recent scientific findings, each of the written comments, as well as to public comments received at several national, international, and U.S. Department of Health and Human Services sponsored workshops. These meetings constituted critically important public forums for discussing the scientific, public health, and social issues attendant to xenotransplantation.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Xenotransplantation Protocol Issues

Xenotransplantation Team

The development and implementation of xenotransplantation clinical research protocols require expertise in the infectious diseases of both human recipients and source animals. Consequently, in addition to health care professionals who have clinical experience with transplantation, the xenotransplantation team should include as active participants:(1) infectious disease physician(s) with expertise in zoonoses, transplantation, and epidemiology; (2) veterinarian(s) with expertise in the animal husbandry issues and infectious diseases relevant to the source animal; (3) specialist(s) in hospital epidemiology and infection control; and (4) experts in research and diagnostic microbiology laboratory methodologies. The sponsor should ensure that the appropriate expertise is available in the development and implementation of the clinical protocol, including the onsite follow up of the xenotransplantation product recipient.

Clinical Xenotransplantation Site

Any sites performing xenotransplantation clinical procedures should have experience and expertise with and facilities for any comparable allotransplantation procedures.

All xenotransplantation clinical centers should utilize CLIA'88 (U.S. Clinical Laboratory Improvements Act, amended in 1988) accredited virology and microbiology laboratories.

The safe conduct of xenotransplantation clinical trials should include the active participation of laboratories with the ability to isolate and identify unusual and/or newly recognized pathogens of both human and animal origin. Each protocol will present unique diagnostic, surveillance, and research needs that require expertise and experience in the microbiology and infectious diseases of both animals and humans. The sponsor should ensure that persons and centers with appropriate experience and expertise are involved in the study development, clinical application, and follow up of each protocol, either on-site or through formal and documented off-site collaborations.

Clinical Protocol Review

All clinical trials involving xenotransplantation are subject to regulation by the U.S. Food and Drug Administration (FDA) under the U.S. Public Health Service Act and the U.S. Federal Food, Drug, and Cosmetic Act.

Sponsors are responsible for ensuring reviews by local review bodies as appropriate, (Institutional Review Boards [IRBs], Institutional Animal Care and Use Committees [IACUCs], Institutional Biosafety Committees [IBCs]), the Food and Drug Administration and the Secretary´s Advisory Committee on Xenotransplantation (SACX) (upon implementation by the Secretary, Health and Human Services [HHS]). (The scope and process for the Secretary´s Advisory Committee on Xenotransplantation review will be described in subsequent publications.)

Institutional review of xenotransplantation clinical trial protocols should address: (1) the potential risks of infection for the recipient and contact populations (including health care providers, family members, friends, and the community at large); (2) the conditions of source animal husbandry (e.g., screening program, animal quarantine); and (3) issues related to human and veterinary infectious diseases (including virology, laboratory diagnostics, epidemiology, and risk assessment).

Health Screening and Surveillance Plans

Clearly defined methodologies for pre-xenotransplantation screening for known infectious agents and post-xenotransplantation surveillance are essential parts of clinical xenotransplantation trials and should be clearly developed in all protocols. Pre-xenotransplantation screening includes screening of the source herd, the source animal(s), and the nonhuman animal live cells, tissues or organs used in the manufacture of the xenotransplantation product or the product itself. Post-xenotransplantation surveillance includes surveillance of the recipient(s) selected health care workers or other contacts, and the surviving source animal(s). The screening methods used and the specific agents sought will differ depending on the procedure, cells, tissue, or organ used, the source animal, and the clinical indication for xenotransplantation. Details of these screening and surveillance plans, including a summary of the relevant aspects of the health maintenance and surveillance program of the herd and the medical history of the source animal(s) and written protocols for hospital infection control practices regarding both xenotransplantation product recipients and health care workers should be described in the materials submitted for review by the Secretary´s Advisory Committee on Xenotransplantation, the Food and Drug Administration, and the local review bodies.

Informed Consent and Patient Education Processes

In the process of obtaining and documenting informed consent, the sponsor and investigators should comply with all applicable regulatory requirement(s) (e.g., Title 45 Code of Federal Regulations Part 46; Title 21 U.S. Code of Federal Regulations Parts 50 and 56), and should adhere to good clinical practices and to the ethical principles derived from the Belmont Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and

to recommendations from the National Bioethics Advisory Board (NBAC). The local Institutional Review Board may consider having the consent process observed by a patient advocate. In addition, the sponsor should ensure that counseling regarding behavior modification and other issues associated with risk of infection is provided to the patient and made available to the patient's family and contacts prior to and at the time of consent. Such counseling should remain available on an ongoing basis thereafter.

The informed consent discussion, the informed consent document, and the written information provided to potential xenotransplantation product recipients should address, at a minimum, the following points relating to the potential risk associated with xenotransplantation:

- The potential for infection with zoonotic agents known to be associated with the nonhuman source animal species.
- The potential for transmission to the recipient of unknown xenogeneic infectious agents. The patient should be informed of the uncertainty regarding the risk of infection, whether such infections might result in disease, the nature of disease that might result, and the possibility that infections with these agents may not be recognized for an extended period of time.
- The potential risk for transmission of xenogeneic infectious agents (and possible subsequent manifestation of disease) to the recipient's family or close contacts, especially sexual contacts. The recipient should be informed that immunocompromised persons may be at increased risk of xenogeneic infections. The recipient should be counseled regarding behavioral modifications that diminish the likelihood of transmitting infectious agents and relevant infection control practices.
- The informed consent process should include a documented procedure to inform the recipient of the responsibility to educate his/her close contacts regarding the possibility of xenogeneic infections from the source animal species and to offer the recipient assistance with this education process, if desired. Education of close contacts should address the uncertainty regarding the risks of xenogeneic infections, information about behaviors known to transmit infectious agents from human to human (e.g., unprotected sex, breast-feeding, intravenous drug use with shared needles, and other activities that involve potential exchange of blood or other body fluids) and methods to minimize the risk of transmission. Recipients should educate their close contacts about the importance of reporting any significant unexplained illness through their health care provider to the research coordinator at the institutions where the xenotransplantation was performed.
- The potential need for isolation procedures during any hospitalization (including to the extent possible the estimated duration of such confinement and the specific symptoms/situation that would prompt such isolation), and any specialized precautions needed to minimize acquisition or transmission of infections following hospital discharge.
- The potential need for specific precautions following hospital discharge to minimize the risk that livestock of the source animal species and the recipient of the xenotransplantation product will represent biohazards to each other. For example, if a recipient comes into contact with the animal species from which the xenotransplantation product was procured, the xenotransplantation product (and therefore the recipient) may have an increased risk from exposures to agents infectious for the xenotransplantation product source

species. Conversely, the recipient may represent a biohazard to healthy livestock if the presence of the xenotransplantation product enables the recipient to serve as a vector for outbreaks of disease in source species livestock.

- The importance of complying with long-term or life-long surveillance necessitating routine physical evaluations and the archiving of tissue and/or body fluid specimens for public health purposes even if the experiment fails and the xenotransplantation product is rejected or removed. The schedule for clinical and laboratory monitoring should be provided to the extent possible. The patient should be informed that any serious or unexplained illness in themselves or their contacts should be reported immediately to the clinical investigator or his/her designee.
- The responsibility of the xenotransplantation product recipient to inform the investigator or his/her designee of any change in address or telephone number for the purpose of enabling long-term health surveillance.
- The importance of a complete autopsy upon the death of the xenotransplantation product recipient, even if the xenotransplantation product was previously rejected or removed. Advance discussion with the recipient and his/her family concerning the need to conduct an autopsy is also encouraged in order to ensure that the recipient's intent is known to all relevant parties.
- The long-term need for access by the appropriate public health agencies to the recipient's medical records. To the extent permitted by applicable laws and/or regulations, the confidentiality of medical records should be maintained. The informed consent document should include a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.
- As an interim precautionary measure, xenotransplantation product recipients and certain of their contacts should be deferred indefinitely from donation of whole blood, blood components, including source plasma and source leukocytes, tissues, breast milk, ova, sperm, or any other body parts for use in humans. Pending further clarification, contacts to be deferred from donations should include persons who have engaged repeatedly in activities that could result in intimate exchange of body fluids with a xenotransplantation product recipient. For example, such contacts may include sexual partners, household members who share razors or toothbrushes, and health care workers or laboratory personnel with repeated percutaneous, mucosal, or other direct exposures. These recommendations may be revised based on ongoing surveillance of xenotransplantation product recipients and their contacts to clarify the actual risk of acquiring xenogeneic infections, and the outcome of deliberations between the Food and Drug Administration and its advisors.

  The Food and Drug Administration has published a draft guidance document ("Guidance for Industry: Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products from Xenotransplantation Product Recipients and Their Contacts") for public comment and will consult with its advisors to identify the range of xenotransplantation products for which recipients and/or certain of their contacts should be recommended for deferral from blood donation. Additionally, the range of contacts who should be deferred from blood donation will be clarified after further public discussion.

- Xenotransplantation product recipients who may wish to consider reproduction in the future should be aware that a potential risk of transmission of xenogeneic infectious agents not only to their partner but also to their offspring during conception, embryonic/fetal development and/or breast-feeding cannot be excluded.
- All centers where xenotransplantation procedures are performed should develop appropriate xenotransplantation procedure-specific educational materials to be used in educating and counseling both potential xenotransplantation product recipients and their contacts. These materials should describe the xenotransplantation procedure(s), and the known and potential risks of xenogeneic infections posed by the procedure(s) in appropriate language. Those activities that are considered to be associated with the greatest risk of transmission of infection to contacts should be described. Education programs should detail the circumstances under which the use of personal protective equipment (e.g., gloves, gowns, masks) or special infection control practices are recommended, and emphasize the importance of hand washing. The potential for transmission of these agents to the general public should be discussed.

Animal Sources for Xenotransplantation

Recognized zoonotic infectious agents and other organisms present in animals, such as normal flora or commensals, may cause disease in humans when introduced by xenotransplantation, especially in immunocompromised patients. The risk of transmitting xenogeneic infectious agents is reduced by procuring source animals from herds or colonies that are screened and qualified as free of specific pathogenic infectious agents and that are maintained in an environment that reduces exposure to vectors of infectious agents. Precautions intended to reduce risk should be employed in all steps of production (e.g., during animal husbandry, procurement and processing of nonhuman animal live cells, tissues or organs used in the manufacture of xenotransplantation products) and should be appropriate to each xenotransplantation protocol. Before an animal species is used as a source of xenotransplantation product(s), sponsors should adequately address the public health issues raised. These issues are delineated in more detail below.

Procedures should be developed to identify incidents that negatively affect the health of the herd. This information is relevant to the safety review of every xenotransplantation product application. Such information, as well as the procedures to collect the information, should be reported to the Food and Drug Administration.

Some experts consider that nonhuman primates pose a greater risk of transmitting infections to humans. The Public Health Service (PHS) recognized the substantial concerns about this issue that have been raised within the scientific community and the general public. In its April 6, 1999 guidance on nonhuman primate xenotransplantation products ("Guidance for Industry: Public Health Issues Posed by the Use of Nonhuman Primate Xenografts in Humans"), the Food and Drug Administration concluded, after consulting with other Public Health Service agencies, that at the current time there is not sufficient information to assess the risks posed by nonhuman primate xenotransplantation. The Food and Drug Administration has determined that:

"...(1) an appropriate federal advisory committee, such as the Secretary's Advisory Committee on Xenotransplantation (SACX) currently under development within the Department of Health and Human Services (DHHS), should address novel protocols and issues raised by the use of nonhuman primate xenografts, conduct discussions, including public discussions as appropriate, and make recommendations on the questions of whether and under what conditions the use of nonhuman primate xenografts would be appropriate in the United States.

(2) clinical protocols proposing the use of nonhuman primate xenografts should not be submitted to Food and Drug Administration until sufficient scientific information exists addressing the risks posed by nonhuman primate xenotransplantation. Consistent with the Food and Drug Administration´s Investigational New Drug (IND) regulations, any protocol submission that does not adequately address these risks is subject to clinical hold (i.e., the clinical trial may not proceed) due to insufficient information to assess the risks and/or due to unreasonable risk..."

Animal Procurement Sources

All xenotransplantation products pose a risk of infection and disease to humans. Regardless of the species of the source animal, precautions appropriate to each xenotransplantation product protocol should be employed in all steps of production (animal husbandry, procurement and processing of nonhuman animal live cells, tissues or organs) to minimize this risk. Source animal procurement and processing procedures should include, at minimum, the following precautions:

- Cells, tissues, and organs intended for use in xenotransplantation should be procured only from animals that have been bred and reared in captivity and that have a documented, well characterized health history and lineage.
- Source animals should be raised in facilities with adequate barriers, i.e. biosecurity, to prevent the introduction or spread of infectious agents. Animals should also be obtained from herds or colonies with restricted admission of new animals. Such closed herds or colonies should be free of infectious agents that are relevant to the animal species and that may pose risk to the patient and/or the public. An infectious agent may pose risk to the patients and/or public if it can infect, cause disease in, and transmit among humans, or if its ability to infect, cause disease in, or transmit among humans remains inadequately defined. In this regard, persistent viral infections are of particular concern. Source animals should specifically be free of infection with any identifiable exogenous persistent virus. Breeding programs utilizing caesarean derivation of animals reduce the risk of maternal-fetal transmission of infectious agents and should be used whenever possible. The prevalence of exposure to these agents should be documented through periodic surveillance of the herd or colony using serologic and other appropriate diagnostic methodologies.
- Animals from minimally controlled environments such as closed corrals (captive free-ranging animals) should not be used as source animals for xenotransplantation. Such animals have a higher likelihood of harboring

adventitious infectious agents from uncontrolled contact with arthropods and/or other animal vectors.

- Wild-caught animals should not be used as source animals for xenotransplantation.
- Animals or live animal cells, tissues, or organs obtained from abattoirs should not be used for xenotransplantation. Such animals are obtained from geographically divergent farms or markets and are more likely to carry infectious agents due to increased exposure to other animals and increased activation and shedding of infectious agents during the stress of slaughter. In addition, health histories of slaughterhouse animals are usually not available.
- Imported animals or the first generation of offspring of imported animals should not be used as source animals for xenotransplantation unless the animals belong to a species or strain (including transgenic animals) not available for use in the United States and their use is scientifically warranted. In this case, the imported animals should be documented to have been bred and continuously maintained in a manner consistent with the principles in this document. The source animal facility, production process and records are subject to inspection by the Food and Drug Administration (Federal Food, Drug and Cosmetic Act). The United States Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS), Veterinary Services (VS) regulates the importation of all animals and animal-origin materials that could represent a disease risk to United States livestock and poultry. Importation or interstate transport of any animal and/or animal-origin material that may represent such a disease risk requires a United States Department of Agriculture permit. In addition, plans for testing and quarantine of the imported animals as well as health maintenance and surveillance of the herd or colony into which imported animals are introduced should be conducted by a veterinarian who is either specifically trained in or who otherwise has a solid background in foreign animal diseases.
- Source animals from species in which transmissible spongiform encephalopathies have been reported should be obtained from closed herds with documented absence of dementing illnesses and controlled food sources for at least two generations prior to the source animal. Xenotransplantation products should not be obtained from source animals imported from any country or geographic region where transmissible spongiform encephalopathies are known to be present in the source species or from which the United States Department of Agriculture prohibits or restricts importation of ruminants or ruminant products due to concern about transmissible spongiform encephalopathies.
- The Centers for Disease Control and Prevention (CDC), Division of Quarantine, regulates the importation of certain animals, including nonhuman primates, because of their potential to cause serious outbreaks of communicable disease in humans. Importers must register with Centers for Disease Control and Prevention, certify imported nonhuman primates will be used only for scientific, educational, and exhibition purposes, implement disease control measures, maintain records regarding each shipment, and report suspected zoonotic illness in animals or workers.

  Further, the importation and/or transfer of known or potential etiological agents, hosts, or vectors of human disease (including biological materials) may require a permit issued by Centers for Disease Control and Prevention´s Office of Health and Safety.

Source Animal Facilities

Potential source animals should be housed in facilities built and operated taking into account the factors outlined in this section.

Source animal facilities (facilities providing source animals for xenotransplantation) should be designed and maintained with adequate barriers to prevent the introduction and spread of infectious agents. Entry and exit of animals and humans should be controlled to minimize environmental exposures/inadvertent exposure to transmissible infectious agents. Source animal facilities should not be located in geographic proximity to manufacturing or agricultural activities that could compromise the biosecurity of these facilities.

Source animal facilities should have veterinarians on staff who possess expertise in the infectious diseases prevalent in the animal species and the emergency clinical care of the species. Facilities should also have persons with expertise in research virology and microbiology either on staff or as established consultants. These facilities should also maintain active and documented collaboration with accredited microbiology laboratories.

Procedures should be in place to assure the humane care of all animals (see e.g., the U.S. Animal Welfare Regulations as amended in 1985 and the U.S. Public Health Service Policy on the Humane Care and Use of Laboratory Animals).

Source animal facilities should incorporate procedures consistent with those set forth for accreditation by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International) and should be consistent with the National Research Council's Guide for the Care and Use of Laboratory Animals (1996).

Source animal facilities should have a documented health surveillance system.

The source animal facility standard operating procedures should thoroughly describe the following: (1) criteria for animal admission, including sourcing and entry procedures, (2) description of the disease monitoring program, (3) criteria for the isolation or elimination of diseased animals, including a diagnostic algorithm for ill and dead animals, (4) facility cleaning and disinfecting arrangements, (5) the source and delivery of feed, water and supplies, (6) measures to exclude arthropods and other animals, (7) animal transportation, (8) dead animal disposition, (9) criteria for the health screening and surveillance of humans entering the facility, and (10) permanent individual animal identification.

- Animal movement through the secured facility should be described in the standard operating procedures of the facility. All animals introduced into the source colony other than by birth should go through a well-defined quarantine and testing period. With regard to the reproduction and raising of suitable replacement animals, the use of methods such as artificial insemination (AI), embryo transfer, medicated early weaning, cloning, or hysterotomy/hysterectomy and fostering may minimize further colonization with infectious agents.
- During final screening and qualification of individual source animals and procurement of live cells, tissues or organs for use in xenotransplantation, the

potential for transmission of an infectious agent should be minimized by established standard operating procedures. One method to accomplish this is a step-wise "batch" or "all-in/all-out" method of source animal movement through the facility rather than continuous replacement movement. With the "all-in/all-out" or "batch" method, a cohort of qualified animals is quarantined from the closed herd or colony while undergoing final screening qualification and xenogeneic biomaterial procurement. After the entire cohort of source animals is removed, the quarantine and xenogeneic biomaterial processing areas of the animal facility are then cleaned and disinfected prior to the introduction of the next cohort of source animals.

- The feed components, including any antibiotics or other medicinals or other additives, should be documented for a minimum of two generations prior to the source animal. Pasteurized milk products may be included in feeds. The absence of other mammalian materials, including recycled or rendered materials, should be specifically documented. The absence of such materials is important for the prevention of transmissible spongiform encephalopathies and other infectious agents. Potentially extended periods of clinical latency, severity of consequent disease, and the difficulty in current detection methods highlight the importance of eliminating risk factors associated with transmissible spongiform encephalopathies.

The sponsor should establish records linking each xenotransplantation product recipient with the relevant health history of the source animal, herd or colony, and the specific organ, tissue, or cell type included in the xenotransplantation product or used in the manufacture of the xenotransplantation product. The relevant records include information on the standard operating procedures of the animal procurement facility, the herd health surveillance, and the lifelong health history of the source animal(s) for the xenotransplantation product.

- The sponsor should maintain these record systems and an animal numbering or other system that allows easy, accurate, and rapid linkage between the information contained in these different record systems and the xenotransplantation product recipient for 50 years beyond the date of xenotransplantation. If record systems are maintained in a computer database, electronic back ups should be kept in a secure office facility and back up on hard copy should be routinely performed.
- In the event that the source animal facility ceases to operate, the facility should either transfer all animal health records and specimens to the respective sponsors or notify the sponsors of the new archive site. If the sponsor ceases to exist, decisions on the disposition of the archived records and specimens should be made in consultation with the Food and Drug Administration.

All animal facilities should be subject to inspection by designated representatives of the clinical protocol sponsor and public health agencies. The sponsor is responsible for implementing and maintaining a routine facilities inspection program for quality control and quality assurance.

Pre-xenotransplantation Screening for Known Infectious Agents

The following points discuss measures for appropriate screening of known infectious agents in the herd, individual source animal and the nonhuman animal

live cells, tissues or organs used in xenotransplantation. The selection of assays for pre-transplant screening should be determined by the source of the nonhuman animal live cells, tissues or organs and the intended clinical application of the xenotransplantation product. General guidance on adventitious agent testing may be found in the document titled â œPoints to Consider for the Characterization of Cell Lines Used to Produce Biologicals,â and a guidance document from the International Conference on Harmonization titled â œQ5D Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Subsets Used for Production of Biotechnological/Biological Products.â

The design of preclinical studies intended to identify infectious agents in the xenotransplantation product and/or the nonhuman animal live cells, tissues or organs intended for use in the manufacture of xenotransplantation products should take into consideration the source animal species and the specific manner in which the xenotransplantation product will be used clinically. These studies should identify infectious agents and characterize their potential pathogenicity and tropism for human cells by appropriate in vivo and in vitro assays. Characterization of persistent viral infections and endogenous retroviruses present in source animals cells, tissues or organs is particularly important. The information from these studies is necessary for the identification and development of appropriate assays for xenotransplantation product screening programs.

Programs for screening and detection of known infectious agents in the herd or colony, the individual source animal, and the xenotransplantation product itself or the nonhuman animal live cells, tissues or organs used in the manufacture of xenotransplantation products should take into account the infectious agents associated with the source animals used, the stringency of the husbandry techniques employed, and the manner in which the xenotransplantation product will be used clinically. These programs should be updated periodically to reflect advances in the knowledge of infectious diseases. The sponsor should develop an adequate screening program in consultation with appropriate experts including oversight and regulatory bodies.

Assays used for screening and detection of infectious agents should have well defined and documented sensitivity, specificity, and reproducibility in the setting in which they are employed. In addition to assays for specific infectious agents, the use of assays capable of detecting broad ranges of infectious agents is strongly encouraged. In vivo assays involving animal models may require different standards for evaluation. Assays under development may complement the screening process.

Samples from the xenotransplantation product itself or of the nonhuman animal live cells, tissues or organs used in the manufacture of the xenotransplantation product, whenever possible, or from an appropriate biologic proxy should be tested preclinically with co-cultivation assays. These assays should include a panel of appropriate indicator cells, which may include human peripheral blood mononuclear cells (PBMC), to facilitate amplification and detection of endogenous retroviruses and other xenogeneic viruses capable of producing infection in humans. Agents that may be latent are of particular concern and their detection may be facilitated by using chemical and irradiation methods.

All xenotransplantation products should be screened by direct culture for bacteria, fungi, and mycoplasma. In addition, universal polymerase chain reaction (PCR) probes for the presence of microorganisms are available and should be considered to complement the screening of xenotransplantation products.

Herd/Colony Health Maintenance and Surveillance

The principal elements recommended to qualify a herd or colony as a source of animals for use in xenotransplantation include: (1) closed herd or colony of stock (optimally caesarian derived) raised in barrier facilities; and (2) adequate surveillance programs for infectious agents. The standard operating procedures of the animal facility with regard to the herd or colony health maintenance and surveillance programs relevant to the specific xenotransplantation product usage should be documented and available to appropriate review bodies. Medical records for the herd or colony and the specific individual source animals should be maintained by the animal facility or the sponsor, as appropriate, for 50 years beyond the date of the xenotransplantation.

Herd or colony health measures that constitute standard veterinary care for the species (e.g., anti-parasitic measures) should be implemented and recorded at the animal facility. For example, aseptic techniques and sterile equipment should be used in all parenteral interventions including vaccinations, phlebotomy, and biopsies. All incidents that may affect herd or colony health should be recorded (e.g., breaks in the environmental barriers of the secured facility, disease outbreaks, or sudden animal deaths). Vaccination and screening schedules should be described in detail and taken into account when interpreting serologic screening tests. Prevention of disease by protection from exposure is generally preferable to vaccination, since this preserves the ability of serologic screening to define herd exposures. In particular, the use of live vaccines is discouraged, but may be justified when dead or acellular vaccines are not available and barriers to exposure are inadequate to prevent the introduction of infectious agents into the herd or colony.

In addition to standard medical care, the herd/colony should be monitored for the introduction of infectious agents that may not be apparent clinically. The sponsor should describe the monitoring program, including the types and schedules of physical examinations and laboratory tests used in the detection of all infectious agents, and document the results.

Routine testing of closed herds or colonies in the United States should concentrate on zoonoses known to exist in captive animals of the relevant species in North America. Since many important pathogens are not endemic to the United States or have been found only in wild-caught animals, testing of breeding stock and maintenance of a closed herd or colony reduces the need for extensive testing of individual source animals. Herd or colony geographic locations are relevant to consideration of presence and likelihood of pathogens in a given herd or colony. The geographic origin of the founding stock of the colony, including quarantine and screening procedures utilized when the closed colony was established, should be taken into consideration. Veterinarians familiar with the prevalence of different infectious agents in the geographic area of source animal origin and the location where the source animals are to be maintained should be consulted.

- As part of the surveillance program, routine serum samples should be obtained from randomly selected animals representative of the herd or colony population. These samples should be tested for indicators of infectious agents relevant to the species and epidemiologic exposures. Additional directed serologic analysis, active culturing, or other diagnostic laboratory testing of individual animals should be performed in response to clinical indications. Infection in one animal in the herd justifies a larger clinical and epidemiologic evaluation of the rest of the herd or colony. Aliquots of serum samples collected during routine surveillance and specific disease investigations should be maintained for 50 years beyond the date of sample collection. The source animal facility or the sponsor should maintain these specimens (either on- or off-site) for investigations of unexpected diseases that occur in the herd, colony, individual source animals, or animal facility staff. These herd health surveillance samples, which are not archived for Public Health Service investigation purposes, should nonetheless be made available to the Public Health Service if needed.
- Any animal deaths, including stillbirths or abortions, where the cause is either unknown or ambiguous should lead to full necropsy and evaluation for infectious etiologies (including transmissible spongiform encephalopathies) by a trained veterinary pathologist. Results of these investigations should be documented.

Standard operating procedures that include maintenance of a subset of sentinel animals are encouraged. Monitoring of these animals will increase the probability of detection of subclinical, latent, or late-onset diseases such as transmissible spongiform encephalopathies.

Individual Source Animal Screening and Qualification

The qualification of individual source animals should include documentation of breed and lineage, general health, and vaccination history, particularly the use of live and/or live attenuated vaccines. The presence of pathogens that result in acute infections should be documented and controlled by clinical examination and treatment of individual source animals, by use of individual quarantine periods that extend beyond the incubation period of pathogens of concern, and by herd surveillance indicating the presence or absence of infection in the herd from which the individual source animal is selected. The use of any drugs or biologic agents for treatment should be documented. During quarantine and/or prior to procurement of live cells, tissues or organs for use in xenotransplantation, individual source animals should be screened for infectious agents relevant to the particular intended clinical use of the planned xenotransplantation product. The screening program should be guided by the surveillance and health history of the herd or colony.

In general, individual source animals should be quarantined for three weeks prior to procurement of live cells, tissues or organs for use in xenotransplantation. During the quarantine, acute illnesses due to infectious agents to which the animal may have been exposed shortly before removal from the herd or colony would be expected to become clinically apparent. It may be appropriate to modify the need for and duration of individual quarantine periods depending on the characterization and surveillance of the source animal herd or colony, the design of the facility in which the herd is bred and maintained, and the clinical urgency.

When the quarantine period is shortened or eliminated, justification should be documented and any potentially increased infectious risk should be addressed in the informed consent document.

- During the quarantine period, candidate source animals should be examined by a veterinarian and screened for the presence of infectious agents (bacteria including rickettsiae when appropriate, parasites, fungi, and viruses) by appropriate serologies and cultures, serum clinical chemistries (including those specific to the function of the organ or tissue to be procured), complete blood count and peripheral blood smear, and fecal exam for parasites. Evaluation for viruses that may not be recognized zoonotic agents but which have been documented to infect either human or nonhuman primate cells in vivo or in vitro should be considered. Particular attention should be given to viruses with demonstrated capacity for recombination, complementation, or pseudotyping. Surveillance of a closed herd or colony will minimize the additional screening necessary to qualify individual member animals. The nature, timing, and results of surveillance of the herd or colony from which the individual animal is procured should be considered in designing appropriate additional screening of individual animals. These tests should be performed as closely as possible to the date of xenotransplantation while ensuring availability of results prior to clinical use.
- Screening of a candidate source animal should be repeated prior to procurement of live cells, tissues or organs for use in xenotransplantation if a period greater than three months has elapsed since the initial screening and qualification were performed or if the animal has been in contact with other non-quarantined animals between the quarantine period and the time of cells, tissue or organ procurement.
- Transportation of source animals may compromise the microbiologic protection ensured by the closed colony. Careful attention to conditions of transport can minimize disease exposures during shipping. Microbiological isolation of the source animal during transit is critically important. Source animals should be transported using a system that reliably ensures microbiological isolation. Transported source animals should be quarantined for a minimum period of three weeks after transportation, during which time appropriate screening should be performed. The sponsor may propose a shorter quarantine period if appropriate justification (that reflects the level of containment and the duration of the transportation) is provided. When source animals are transported intact, the sponsor should consult the Food and Drug Administration about further details of appropriate transport, quarantine, and screening. If the animals are transported across state or federal boundaries the US Department of Agriculture should be consulted.
- For the reasons cited above, it is preferable, whenever feasible, to procure live cells, tissues or organs for use in xenotransplantation at the animal facility. Precautions employed during transport to ensure microbiological isolation of the procured xenotransplantation product or live cells, tissues or organs should be documented.

All procured cells, tissues and organs intended for use in xenotransplantation should be as free of infectious agents as possible. The use of source animals in which infectious agents, including latent viruses, have been identified should be avoided. However, the presence of an infectious agent in certain anatomic sites,

for example the alimentary tract, should not preclude use of the source animal if the agent is documented to be absent in the xenotransplantation product.

When feasible, a biopsy of the nonhuman animal live cells, tissues or organs intended for use in xenotransplantation, the xenotransplantation product itself, or other relevant tissue should be evaluated for the presence of infectious agents by appropriate assays and histopathology prior to xenotransplantation, and then archived.

The sponsor should ensure that the linked records are available for review when appropriate by the local review bodies, the Secretary´s Advisory Committee on Xenotransplantation (SACX), and the Food and Drug Administration. These records should include information on the results of the quarantine and screening of individual xenotransplantation source animals. In addition to records kept at the Source Animal Facility, a summary of the individual source animal record should accompany the xenotransplantation product and be archived as part of the medical record of the xenotransplantation product recipient.

The source animal facility should notify the sponsor in the event that an infectious agent is identified in the source animal or herd subsequent to procurement of live cells, tissues or organs for use in xenotransplantation (e.g., identification of delayed onset transmissible spongiform encephalopathies in a sentinel animal).

The sponsor should ensure that the quarantine, screening, and qualification program is appropriately tailored to the specific source animal species, the animal husbandry history, the process for procuring the xenogeneic biomaterial and preparing the xenotransplantation product, and the clinical application. The sponsor should also ensure that the results of these procedures are reviewed and approved by persons with the appropriate expertise prior to the clinical application.

Procurement and Screening of Nonhuman Animal Live Cells, Tissues or Organs Used for Xenotransplantation

Procurement and processing of cells, tissues and organs should be performed using documented aseptic conditions designed to minimize contamination. These procedures should be conducted in designated facilities which may be subject to inspection by appropriate oversight and regulatory authorities.

Cells, tissues or organs intended for xenotransplantation that are maintained in culture prior to xenotransplantation should be periodically screened for maintenance of sterility, including screening for viruses and mycoplasma. The Food and Drug Administration publications titled "Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy (1998)"; "Points To Consider in the Characterization of Cell Lines Used to Produce Biologicals (1993)"; and "Points to Consider in the Manufacture and Testing of Therapeutic Products for Human Use Derived from Transgenic Animals (1995)" should be consulted for guidance. The sponsor should develop, implement, and stringently enforce the standard operating procedures for the procurement and screening processes. Procedures that may inactivate or remove pathogens without compromising the integrity and function of the xenotransplantation product should be employed.

All steps involved in the procuring, processing, and screening of live cells, tissues or organs or xenotransplantation products to the point of xenotransplantation should be rehearsed preclinically to ensure reproducible quality control.

If nonhuman animal live cells, tissues or organs for use in xenotransplantation are procured without euthanatizing the source animal, the designated Public Health Service specimens should be archived and the animal's health should be monitored for life. When source animals die or are euthanatized, a complete necropsy with gross, histopathologic and microbiological evaluation by a trained veterinary pathologist should follow, regardless of the time elapsed between xenogeneic biomaterial procurement and death. This should include evaluation for transmissible spongiform encephalopathies. The sponsor should maintain documentation of all necropsy results for 50 years beyond the date of necropsy as part of the animal health record In the event that the necropsy reveals findings pertinent to the health of the xenotransplantation product recipient(s) (e.g., evidence of transmissible spongiform encephalopathies) the finding should be communicated to the Food and Drug Administration without delay.

Archives of Source Animal Medical Records and Specimens

Systematically archived source animal biologic samples and record keeping that allows rapid and accurate linking of xenotransplantation product recipients to the individual source animal records and archived biologic specimens are essential for public health investigation and containment of emergent xenogeneic infections.

Source animal biologic specimens designated for Public Health Service (PHS) use (as outlined below) should be banked at the time of xenogeneic biomaterial procurement. These specimens should remain in archival storage for 50 years beyond the date of the xenotransplantation to permit retrospective analyses if a public health need arises. Such archived specimens should be readily accessible to the Public Health Service and remain linked to both source animal and recipient health records.

At the time of procurement of nonhuman animal live cells, tissues or organs for use in xenotransplantation, plasma should be collected from the source animal and stored in sufficient quantity for subsequent serology and viral testing. In addition, the sponsor should recover and bank sufficient aliquots of cryopreserved leukocytes for subsequent isolation of nucleic acids and proteins as well as aliquots for thawing viable cells for viral co-culture assays or other tissue culture assays. Ideally, at least ten 0.5 cc aliquots of citrated or ethylene diamine tetra acetate (EDTA)-anticoagulated plasma should be banked. At least five aliquots of viable ($1x10^7$) leukocytes should be cryopreserved. It may also be appropriate to collect paraffin-embedded, formalin fixed, and cryopreserved tissue samples from source animal organs relevant to the specific protocol at the time of xenogeneic biomaterial procurement. Additionally, cryopreserved tissue samples representative of major organ systems (e.g., spleen, liver, bone marrow, central nervous system, lung,) should be collected from source animals at necropsy. The material submitted for review by Food and Drug Administration and, when appropriate, the Secretary's Advisory Committee on Xenotransplantation (under development) should justify the types of tissues, cells, and plasma taken for storage and any smaller quantities of plasma and leukocytes collected.

The sponsor should maintain archives of designated Public Health Service specimens and serum collected for herd surveillance for 50 years beyond the date of collection, and animal health records for 50 years beyond the date of the animal's death.

Disposal of Animals and Animal By-products

The need for advanced planning for the ultimate disposition of source and sentinel animals bred for xenotransplantation, especially animals of species ordinarily used to produce food, should be anticipated. Generally, source and sentinel animals should not be used as pets, breeding animals, sources of human food via milk or meat, or as ingredients of feed for other animals because of their potential to enter the human or animal food chain.

There may be species specific situations where animals from xenotransplant facilities can be considered to be safe for human food use or as feed ingredients when disposed of through rendering the Food and Drug Administration´s Center for Veterinary Medicine (CVM) regulates animal feed ingredients and also establishes conditions for the release of animals to the United States Department of Agriculture (USDA) Food Safety Inspection Service for inspection as food for humans. Persons wishing to offer animals into the human food or animal feed supply or who have food safety questions should consult with Center for Veterinary Medicine. Food safety issues will be referred to Center for Veterinary Medicine.

Animals from biomedical facilities that have not been authorized for release by Center for Veterinary Medicine into the human food or animal feed supply may be adulterated under the Federal Food, Drug and Cosmetic Act, unfit for food or feed, and potentially infectious. They should be disposed of in a manner consistent with infectious medical waste in compliance with federal, state and local requirements.

Clinical Issues

Xenotransplantation Product Recipient

Surveillance of the xenotransplantation product recipient

Post-xenotransplantation clinical and laboratory surveillance of xenotransplantation product recipients is critical, as it provides the means of monitoring for any introduction and propagation of xenogeneic infectious agents in the xenotransplantation product recipient. The sponsor should carry out, and ensure documentation of, the surveillance program. Life-long post-xenotransplantation surveillance of xenotransplantation product recipients is appropriate.

Recipients should be evaluated throughout their lifetime for adverse clinical events potentially associated with xenogeneic infections.

Laboratory surveillance of the xenotransplantation product recipient should be instituted when xenogeneic infectious agents are known or suspected to be present in the xenotransplantation product. Minimally, laboratory surveillance

should be conducted for evidence of recipient infection with all identified xenotropic endogenous retroviruses known to be present in the source animal. The intent of active screening in this setting is detection of sentinel human infections prior to dissemination in the general population. Serum, peripheral blood mononuclear cells (PBMCs), tissue or other body fluids should be assayed at intervals post-xenotransplantation for xenogeneic agents known or suspected to be present in the xenotransplantation product. Laboratory surveillance should include frequent screening in the immediate post-xenotransplantation period (e.g., at 2, 4, and 6 weeks after xenotransplantation) that decreases in frequency if evidence of infection remains absent.

It is critical that adequate diagnostic assays and methodologies for surveillance of known infectious agents from the source animal are available prior to initiating the clinical trial. The sensitivity, specificity, and reproducibility of these testing methods should be documented under conditions that simulate those employed at the time of and following the xenotransplantation procedure. As with pre-xenotransplantation screening, assays under development may complement the surveillance process.

The laboratory surveillance should include methods to detect infectious agents known to establish persistent latent infections in the absence of clinical symptoms (e.g., herpes viruses, retroviruses, papillomaviruses) and that are known or suspected to have been present in the xenotransplantation product. When the xenogeneic viruses of concern have similar human counterparts (e.g., simian cytomegalovirus), assays to distinguish between the two should be used in the post-xenotransplantation laboratory surveillance. Depending upon the degree of immunosuppression in the recipient, serological assays may be or may not be useful. Methods for analysis may include co-cultivation of cells coupled with appropriate detection assays.

Xenotransplantation Product Recipients' Biologic Specimens Archived for Public Health Investigations (Public Health Service Specimens)

Biological specimens obtained from the xenotransplantation product recipients and designated for public health investigations (as distinct from specimens collected for clinical evaluation or laboratory surveillance) should be archived for 50 years beyond the date of the xenotransplantation to allow retrospective investigation of xenogeneic infections. The type and quantity of specimens archived may vary with the clinical procedure and the age of the xenotransplantation product recipient. In the application for Food and Drug Administration review, which may also be reviewed by the Secretary´s Advisory Committee on Xenotransplantation (SACX), the sponsor should justify the amount and types of specimens to be designated for Public Health Service use, including any differences from the recommendations described below.

At selected time points, at least three to five 0.5 cc aliquots of citrated or ethylene diamine tetra acetate (EDTA)-anticoagulated plasma should be recovered and archived. At least two aliquots of viable (1×10^7) leukocytes should be cryopreserved. Specimens from any xenotransplantation product that is removed (e.g., post-rejection or at the time of death) should be archived.

The following schedule for archiving biological specimens is recommended: (1) Prior to the xenotransplantation procedure, two sets of samples should be collected and archived one month apart. If this is not feasible then two sets should be collected and archived at times that are separated as much as possible. One set should be collected immediately prior to the xenotransplantation. (2) Additional sets should be archived in the immediate post-xenotransplantation period and at approximately one month and six months after xenotransplantation. (3) Collection should then be obtained annually for the first two years after xenotransplantation. (4) After that, specimens should be archived every five years for the remainder of the recipient's life. More frequent archiving may be indicated by the specific protocol or the recipient's medical course.

In the event of recipient's death, snap-frozen samples stored at –70 degrees C, paraffin embedded tissue, and tissue suitable for electron microscopy should be collected at autopsy from the xenotransplantation product and all major organs relevant to either the xenotransplantation or the clinical syndrome that resulted in the patient's death. These designated Public Health Service specimens should be archived for 50 years beyond the date of collection.

The sponsor should maintain an accurate archive of the Public Health Service specimens. In the absence of a central facility, these specimens should be archived with the safeguards necessary to ensure long-term storage (e.g., a monitored storage freezer alarm system and specimen archiving in split portions in separate freezers) and an efficient system for the prompt retrieval and linkage of data to medical records of recipients and source animals.

The sponsor should maintain these archives and a record system that allows easy, accurate, and rapid linkage of information among the different record systems (i.e., the specimen archive, the recipient's medical records and the records of the source animal) for 50 years beyond the date of xenotransplantation. If record systems are maintained in a computer database, electronic back ups should be kept in a secure office facility and back up on hard copy should be routinely performed.

A clinical episode potentially representing a xenogeneic infection should prompt notification of the Food and Drug Administration, which will notify other federal and state health authorities as appropriate. Under these circumstances, the Public Health Service may decide that an investigation involving the use of these archived biologic specimens is warranted to assess the public health significance of the infection.

Infection Control

Infection control practices

Strict adherence to recommended infection control measures will reduce the risk of transmission of xenogeneic infections and other blood borne and nosocomial pathogens. Standard precautions should be used for the care of all patients. Standard precautions includes hand washing before and after each patient contact, appropriate use of barriers, and care in the use and disposal of needles and other sharp instruments.

Additional infection control or isolation precautions (e.g., airborne, droplet, contact) should be employed as indicated in the judgment of the hospital epidemiologist and the xenotransplantation team infectious disease specialist. For example, appropriate isolation precautions for each hospitalized xenotransplantation product recipient will depend upon the type of xenotransplantation, the extent of immunosuppression, and patient symptoms. Isolation precautions should be continued until a diagnosis has been established or the patient symptoms have resolved. The appropriateness of isolation precautions and other infection control measures should be reassessed when the diagnosis is established, the patient's symptoms change, and at the time of readmission and discharge. Discharge instructions should include specific education on appropriate infection control practices following discharge, including any special precautions recommended for disposal of biologic products. The most restrictive level of isolation should be used when patients exhibit respiratory symptoms because airborne transmission of infectious agents is most concerning.

Health care personnel, including xenotransplantation team members, should adhere to recommended procedures for handling and disinfection/sterilization of medical instruments and disposal of infectious waste.

Biosafety level 2 (BSL-2) standard and special practices, containment equipment and facilities should be used for activities involving clinical specimens from xenotransplantation product recipients. Particular attention should be given to sharps management and bioaerosol containment. Biosafety level-3 standard and special practices and containment equipment should be employed in a biosafety level-2 facility when propagating an unidentified infectious agent isolated from a xenotransplantation product recipient.

Acute Infectious Episodes

Most acute viral infectious episodes among the general population are never etiologically identified. Xenotransplantation product recipients are at risk for these infections and other infections common among immunosuppressed allograft recipients. When the source of an illness in a recipient remains unidentified despite standard diagnostic procedures, it may be appropriate to perform additional testing of body fluid and tissue samples. The infectious disease specialist, in consultation with the hospital epidemiologist, the veterinarian, the clinical microbiologist and other members of the xenotransplantation team should assess each clinical episode and make a considered judgment regarding the significance of the illness, the need and type of diagnostic testing and specific infection control precautions. Other experts on infectious diseases and public health may also need to be consulted.

In immunosuppressed xenotransplantation product recipients, assays of antibody response may not detect infections reliably. In such patients, culture systems, genomic detection methodologies and other techniques may detect infections for which serologic testing is inadequate. Consequently, clinical centers where xenotransplantation is performed should have the capability to culture and to identify viral agents using in vitro and in vivo methodologies either on site or through active and documented collaborations. Specimens should be handled to ensure viability and to maximize the probability of isolation and identification of fastidious agents. Algorithms for evaluation of unknown xenogeneic pathogens

should be developed in consultation with appropriate experts, including persons with expertise in both medical and veterinary infectious diseases, laboratory identification of unknown infectious agents and the management of biosafety issues associated with such investigations.

Acute and convalescent sera obtained in association with acute unexplained illnesses should be archived when judged appropriate by the infectious disease physician and/or the hospital epidemiologist. This would permit retrospective study and perhaps the identification of an etiologic agent.

Health Care Workers

The risk to health care workers who provide post-xenotransplantation care to xenotransplantation product recipients is undefined. However, health care workers, including laboratory personnel, who handle the animal tissues/organs prior to xenotransplantation will have a definable risk of infection not exceeding that of animal care, veterinary, or abattoir workers routinely exposed to the source animal species provided equivalent biosafety standards are employed.

The sponsor should ensure that a comprehensive occupational health services program is available to educate workers regarding the risks associated with xenotransplantation and to monitor for possible infections in workers. The occupational health service program should include:

Education of Health Care Workers. All centers where xenotransplantation procedures are performed should develop appropriate xenotransplantation procedure-specific educational materials for their staff. These materials should describe the xenotransplantation procedure(s), the known and potential risks of xenogeneic infections posed by the procedure(s), and research or health care activities that may pose the greatest risk of infection or nosocomial transmission of zoonotic or other infectious agents. Education programs should detail the circumstances under which the use of standard precautions and other isolation precautions are recommended, including the use of personal protective equipment handwashing before and after all patient contacts, even if gloves are worn. In addition, the potential for transmission of these agents to the general public should be discussed.

Health Care Worker Surveillance. The sponsor and the occupational health service in each clinical center should develop protocols for monitoring health care personnel. These protocols should describe methods for storage and retrieval of personnel records and collection of serologic specimens from workers. Baseline sera (i.e., prior to exposure to xenotransplantation products or recipients) should be collected from all personnel who provide direct care to xenotransplantation product recipients, and laboratory personnel who handle, or are likely to handle, animal cells, tissues and organs or biologic specimens from xenotransplantation product recipients. Baseline sera can be compared to sera collected following occupational exposures; such baseline sera should be maintained for 50 years from the time of collection. The activities of the occupational health service should be coordinated with the infection control program to ensure appropriate surveillance of infections in personnel.

Post-Exposure Evaluation and Management. Written protocols should be in place for the evaluation of health care workers who experience an exposure where there is a risk of transmission of an infectious agent, e.g., an accidental needle stick. Health care workers, including laboratory personnel, should be instructed to report exposures immediately to the occupational health services. The post-exposure protocol should describe the information to be recorded including the date and nature of exposure, the xenotransplantation procedure, recipient information, actions taken as a result of such exposures (e.g., counseling, post-exposure management, and follow-up) and the outcome of the event. This information should be archived in a health exposure log and maintained for at least 50 years from the time of the xenotransplantation despite any change in employment of the health care worker or discontinuation of xenotransplantation procedures at that center. Health care and laboratory workers should be counseled to report and seek medical evaluation for unexplained clinical illnesses occurring after the exposure.

Health Care Records

The sponsor should maintain a cross-referenced system that links the relevant records of the xenotransplantation product recipient, xenotransplantation product, source animal(s), animal procurement center, and significant nosocomial exposures. These records should include: (1) documentation of each xenotransplantation procedure, (2) documentation of significant nosocomial health exposures, and (3) documentation of the infectious disease screening and surveillance records on both xenotransplantation product source animals and recipients. These records should be updated regularly and cross-referenced to allow rapid and easy linkage between the clinical records of the source animal(s) and the xenotransplantation product recipient.

To the extent permitted by applicable laws and/or regulations, the confidentiality of all medical and research records pertaining to human recipients should be maintained.

The documentation of each xenotransplantation procedure includes the date and type of the procedure, the principal investigator(s), the xenotransplantation product recipient, the xenotransplantation product(s), the individual source animal(s) and the procurement facilities for these animals, as well as the health care workers associated with each procedure.

The documentation of significant nosocomial health exposures includes the persons involved, the date and nature of each potentially significant nosocomial exposure, and the actions taken.

The documentation of infectious disease screening and surveillance includes: (a) a summary of the source animal(s) health status; (b) the results of the pre-xenotransplantation screening program for the source animal(s); (c) the results of the pre-xenotransplantation screening program for the xenotransplantation product; (d) the post-xenotransplantation surveillance studies on the xenotransplantation product recipient; and (e) a summary of significant relevant post-xenotransplantation clinical events.

Public Health Needs

National Xenotransplantation Database

A pilot project to demonstrate the feasibility of, and identify system requirements for a National Xenotransplantation Database is currently underway. It is anticipated that this pilot would be expanded into a fully operational database to collect data from all clinical centers conducting trials in xenotransplantation and all animal facilities providing animals or xenogeneic organs, tissues, or cells for clinical use. Such a database would enable: (a) the recognition of rates of occurrence and clustering of adverse health events, including events that may represent outcomes of xenogeneic infections; (b) accurate linkage of these events to exposures on a national level; (c) notification of individuals and clinical centers regarding epidemiologically significant adverse events associated with xenotransplantation; and (d) biological and clinical research assessments. When such a database becomes functional, the sponsor should ensure that information requested by the database is provided in an accurate and timely manner. To the extent allowed by law, information derived from the database would be available to the public with appropriate confidentiality protections for any proprietary or individually identifiable information.

Biologic Specimen Archives

The sponsor should ensure that the designated Public Health Service specimens from the source animals, xenotransplantation products, and xenotransplantation product recipients are archived. The biologic specimens should be collected and archived under conditions that will ensure their suitability for subsequent public health purposes, including public health investigations. The location and nature of archived specimens should be documented in the health care records and this information should be linked to the National Xenotransplantation Database when the latter becomes functional.

The Department of Health and Human Services is considering options for a central biological archive, e.g., one maintained by a private sector organization under contract to the Department of Health and Human Services. Designated Public Health Service specimens would be deposited in such a repository.

Secretary's Advisory Committee on Xenotransplantation (SACX)

The Secretary´s Advisory Committee on Xenotransplantation is currently being implemented by the Department of Health and Human Services. As currently envisioned, the Secretary´s Advisory Committee on Xenotransplantation will consider the full range of complex issues raised by xenotransplantation, including ongoing and proposed protocols, and make recommendations to the Secretary on policy and procedures. The Secretary´s Advisory Committee on Xenotransplantation will also provide a forum for public discussion of issues when appropriate. These activities will facilitate the Department of Health and Human Services´ efforts to develop an integrated approach to addressing emerging public health issues in xenotransplantation. The structure and functions of the Secretary´s Advisory Committee on Xenotransplantation as well as procedures for Secretary´s Advisory Committee on Xenotransplantation review of protocols and issues will be described in subsequent publications. Inquiries about the status and function of, and access to the Secretary´s Advisory Committee on Xenotransplantation should be directed to the Office of Science Policy, Office of

the Secretary, Department of Health and Human Services, or the Office of Biotechnology Activities (OBA), formerly known as the Office of Recombinant DNA Activities (ORDA), Office of the Director, National Institutes of Health (NIH).

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Minimize the risk of zoonotic infection of xenotransplantation product recipients.
- Minimize the risk of subsequent transmission of zoonotic infection to recipients´ families, healthcare workers and other close contacts, and the general public.

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This guidance document represents the U.S. Public Health Service's (PHS) current thinking on certain infectious disease issues in xenotransplantation. It does not create or confer any rights for or on any person and does not operate to bind U.S. Public Health Service or the public. This guidance is not intended to set forth an approach that addresses all of the potential health hazards related to infectious disease issues in xenotransplantation nor to establish the only way in which the public health hazards that are identified in this document may be addressed. The U.S. Public Health Service acknowledges that not all of the recommendations set forth within this document may be fully relevant to all xenotransplantation products or xenotransplantation procedures. Sponsors of clinical xenotransplantation trials are advised to confer with relevant authorities (the Food and Drug Administration [FDA], other reviewing authorities, funding sources, etc.) in assessing the relevance and appropriate adaptation of the general guidance offered here to specific clinical applications.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Staying Healthy

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

U.S. Public Health Service guideline on infectious disease issues in xenotransplantation. Centers for Disease Control and Prevention. MMWR Recomm Rep 2001 Aug 24;50(RR-15):1-46. [131 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2001 Aug 24

GUIDELINE DEVELOPER(S)

Centers for Disease Control and Prevention - Federal Government Agency [U.S.]
Department of Health and Human Services (U.S.) - Federal Government Agency [U.S.]
Food and Drug Administration (U.S.) - Federal Government Agency [U.S.]
Health Resources and Services Administration - Federal Government Agency [U.S.]
National Institutes of Health (U.S.) - Federal Government Agency [U.S.]
Public Health Service (U.S.) - Federal Government Agency [U.S.]

SOURCE(S) OF FUNDING

United States Government

GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Not stated

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

An update is not in progress at this time.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Centers for Disease Control and Prevention (CDC) Web site.

Print copies: Available from the Centers for Disease Control and Prevention, MMWR, Atlanta, GA 30333. Additional copies can be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402-9325; (202) 783-3238.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on November 9, 2001.

COPYRIGHT STATEMENT

Planning and Evaluation, Office of the Secretary, U.S. Department of Health and Human Services.)

Date Modified: 11/15/2004